DETAILED ACTION

1. Applicant's amendment, filed on June 20, 2011, is entered.

Claims 6-8 have been canceled.

Claims 16 and 17 have been added.

Claims 10-12 and newly added claim 17 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 6, 2008.

Claims 1-5, 9, 13-15, and newly added claim 16 are currently under consideration as they read on originally elected invention of a sugar chain-altered anti-HM1.24 antibody.

2. In view of applicant's amendment, only following rejections have been set forth herein.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. This is a **New Ground of Rejection** necessitated by applicant's amendment to the claims. Claims 1-5, 9, and 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5, 9, and 13-16 are indefinite in the recitation of "A sugar chain-altered antibody (anti-HM1.24 antibody) against HM1.24 antigen, ... wherein said sugar chain does not contain α1,6, core fucose but contains a bisecting N-acetylglucosamine (GlcNac)....,

wherein of all sugar chains on said antibody the relative ration of all fucose-free sugar chains is 30% or more" because the metes and bounds of the claims are unclear and ambiguous. The specification only discloses α1,6, core fucose in N-glycan attached to position 297 of the antibody. If the sugar chain altered antibody does not contain α1,6, core fucose, then the antibody does not contain fucose. Thus, the relative fucose-free sugar chain is 100% (meaning no fucose on the antibody) rather than 30% or more. As such, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

For examination and applying prior art purposes, the percentage recited in the wherein clause is read as in an antibody composition rather than a single antibody.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-5, 9, 13-15, and newly added claim 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "wherein of all sugar chains on said antibody the relative ration of all fucose free sugar chain is 30% or more" recited in independent claim 1 is not supported by the original disclosure or claim as filed.

The phrase "wherein the percentage of sugar chains with bisecting GlcNAc is about 11%" recited in newly added claim 16 is not supported by the original disclosure or claim as filed.

Applicant's amendment, filed on June 20, 2011, directs to support to page 3 of the specification for the amendment in independent claim 1 and Table 1 in the specification for the newly added claim 16 and asserts that no new matter has been added.

However, the specification as filed does not provide sufficient written description of the above-mentioned "limitations". The specification discloses a composition comprising an anti-HM1.24 antibody having a fucose-free sugar chain, wherein the relative ration of the fucose-free sugar chain is 30% or 35% or more in the composition. This is different from the recitation in independent claim 1 which is drawn to a single antibody comprising a N-linked sugar chain without fucose, wherein of all sugar chains on the single antibody the relative ration of all fucose-free sugar chains is 30% or more. In addition, Table 1 on page 19 of the specification does not disclose the percentage of sugar chains with bisecting GlcNAc is about 11%.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1-5, 9, 13-15, and newly added claim 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Kanda et al. (US Patent Application 2003/0115614, reference on PTO-892 mailed on January 9, 2008) for reasons of record.

Applicant's arguments have been fully considered but have not been found persuasive.

Applicant argues that Kanda et al. teach anti-HM1.24 antibody among a laundry list of antibodies without reduction to practice of the anti-HM1.24 antibody.

This is not found persuasive for following reasons:

Contrary to applicant's assertion, it is noted that a reference that clearly names the claimed species anticipates the claim no matter how many other species are named (see MPEP 2123.02). In this case, Kanda et al. clearly discloses the anti-HM1.24 antibody. Thus, the reference teaching would encompass the antibody.

Applicant further argues that Kanda et al. demonstrate that the claimed glycosylation is not produced. Applicant once again asserts that Kanda et al. do not teach a sugar chain with bisecting GlcNAc containing no α1,6 core fucose. Applicant states that Tables 1 and 2 of Kanda et al. shows that 47% of sugar chains from YB2/0 cells are fucosylated. Applicant asserts Example 11 of Kanda et al. describe an experiment to examine the effect of fucosyltransferase (FUT8) on antibody glycosylation and clearly teach that that fucosyltransferase overexpressing cells produced an antibody with fucosylated bisecting GlcNAc. Thus, applicant asserts Kanda et al. do not anticipate the instant invention.

This is not found persuasive for following reasons:

Contrary to applicant's assertion that Kanda's antibody produced in YB2/0 does not contain the N-glycan structure as instantly claimed, it is noted that applicant has not provided any objective evidence to show the reasons why the prior art antibody produced in the same YB2/0 host cells as the instant antibody would not have the same N-glycan structure. Table 1 of Kanda et al. showing 47% of sugar chains from wild type YB2/0 cells are fucosylated which would meet the fucose-free sugar chain percentage (30% or more or 35 % or more) required by the instant claims. There is no objective evidence that anti-HM1.24 antibody produced in the YB2/0 taught by Kanda et al. would not have the same sugar chain structure recited in the instant claims. Regarding Example 11 in the prior art, FUT8 overexpressing cells would obviously produce fucosylated bisecting GlcNAc as disclosed by Kanda et al. (e.g. column 96). Kanda et al. uses Example 11 with host cells overexpressing fucosyltransferase (FUT8) to prove the point

that the content of α1,6 core fucose of an antibody correlates with the level of FUT8 expressed (see column 96). Therefore, applicant's arguments relying upon Example 11 are not persuasive since applicant has not shown that FUT8 knock-out host cells including YB20/FUT8 knock-out as claimed by Kanda et al. would not produce an anti-HM1.24 antibody having the same N-glycan structure as claimed. Given that the sugar chain structures as claimed is determined by the host cells used to produce antibody, and given that the prior art antibody is produced in the same host cells or improved (with fucosyltransferase gene being knock-out) as those used in the instant application, the prior art antibody would inherently have the sugar chain structure as claimed, especially absent of evidence of contrary. Therefore, applicant's arguments have not been found persuasive.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-5, 9, 13-15, and newly added claim 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ono et al. (US 6,699,974, reference of the record) in view of Umana et al. (US 6,602,684, reference of record) as evidenced by the instant disclosure of host cell

expressing GnT III (e.g. in CHO cells) for making the claimed HM1.24 antibody in page 11 and pages 22-23 of the instant specification for the reasons of record.

The previous Office Action states:

"*Ono et al. teach humanized anti-HM1.24 antibodies exhibiting effector functions including antibody dependent cell mediated cytotoxicity (ADCC) is therapeutically effective to treat B cell malignancy (e.g. see claims 1-9 and columns 37-70).*

The reference teachings differ from the claimed invention by not describing a sugar chain altered anti-HM1.24 antibody.

Umana et. al. teach that therapeutical antibodies relying upon effector functions (e.g. ADCC) can be produced in glycosylation engineered host cells wherein the host cells express β1,4 N-acetylglucosaminyltransferase (GnT III) for increased ADCC function (e.g. see claims 1-10). Further, Umana et al. characterized the N-glycan of said antibodies to be Manβ1-4GlcNAcβ1-4GlcNAc core structure and without core fucose but have bisecting GlcNAc (e.g. see Figures 9-11). Furthermore, Umana et al. teach that antibodies produced in the engineered host cells expressing GnT III have higher accumulation of non-fucosylated bisecting sugar chain because N-linked oligosaccharides which are first modified by GnT III can no longer be biosynthetic substrates for core α1,6-fucosylaltransferase (e.g. see column 26 and Figures 9-11). Umana et al. teach that said antibody having altered glycoform exhibits improved therapeutic properties via enhanced ADCC function (e.g. see column 2).

It would thus be obvious to one of skill in the art to produce humanized anti-HM1.24 antibody taught by Ono et al. using GnT III engineered host cells taught by Umana et al. because anti-HM1.24 antibody exhibiting ADCC function is therapeutically effective in treating B cell malignancy and antibodies produced in GnTIII engineered host cells would have altered glycan structure, which in term, exhibits enhanced ADCC function. One of ordinary artisan would have been motivated to do so because Ono et al. teach that humanized anti-HM1.24 antibody with ADCC function is therapeutically effective in treating B cell lymphoma and Umana et al. teach methods of increasing ADCC function of therapeutic antibody by alter it N-glycan structure.

As evidenced by the instant disclosure, the claimed antibody can be produced in host cells engineered to express GnT III enzyme (see pages 11 and 22-23 of the instant specification). Thus, the humanized anti-HM1.24 antibody produced in Umana's host cells engineered in the same manner as the instant application (expressing GnT III) would be expected to have the same N-glycan structure as the instant claims.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary."

Applicant's arguments, filed on June 20, 2011, have been fully considered but have not been found persuasive.

Applicant argues that as taught by Kanda, the only bisected antibody modified by GnTIII was also fucosylated and Umana et al. also report numerous bisecting fucosylated antibodies. Applicant argues that Figure 11 of Umana et al. shows that the nonfucosylated structure to be, e.g. Man4GnbG or Man5GnGnb which do not read on the instant claims 13-15. Applicant asserts that the glycosylation patterns taught by Umana et al. differ from the instant application. Specifically, applicant states:

> "*Yet further, the glycosylation patterns identified by Applicants differ from those in Umana. For example, the dominant species identified at the lowest level of GnTIII expression is fucosylated M3Gn2 (m/z 1486), which constitutes almost 50% of species. By comparison, in Applicant's specification this species (equivalent to sugar chain E on Figure 1) comprise approximately 23 % (Table 1). In addition, m/zl 339 corresponds to unfucosylated M3Gn2, which are the lowest level in Figure 9 around 1%, and increases to maximal 5%. This species is equivalent to sugar chain A in Applicant's specification, and constitutes around 18% of all sugar chains (see Table 1). The general differences in glycosylation patterns call into doubt the degree to which Umana can be relied upon for the obviousness rejection. The Rejection relies on the reasoning in Umana for the obviousness rejection, yet ignores the many factual differences between Umana and Applicant's specification that show flaws in Umana's reasoning.*"

Applicant asserts since Umana et al. do not teach or suggest of all sugar chains on the antibody, the relative ratio of fucose-free sugar chains is 30% or more, Umana et al. is not concerned with the presence or absence of fucsose but only bisected oligosaccharides.

Therefore, applicant asserts the rejection should be withdrawn.

This is not found persuasive for following reasons:

Contrary to applicant's arguments that Umana et al. do not teach antibody with the sugar chain structure as claimed, it is noted that applicant has not provided any objective evidence as to why that prior art antibody produced in the same manner as the instant application would not inherently have the same N-glycan structure as the instant claims. The problem here is that the Umana et al. teach a method of producing antibody with high effector functions including ADCC

by modifying the glycosylation patterns of the antibody using GnTIII overexpressing CHO cells which is how the instant specification produces the claimed antibody (e.g. see pages 11 and 22-23). Given that the instant antibody and the prior art antibody are produced in the same manner using the same type of modified host cells (CHO overexpressing GnTIII) which determines the N-glycan structures of the antibodies, the prior art antibody would inherently has the same N-glycan structure as the instant claims absent evidence of contrary. Further, as applicant asserts that Umana et al. teach that the dominant species identified at the lowest level of GnTIII expression is fucosylated M3Gn2 (m/z 1486), which constitutes almost 50% of species, in turn, the unfucosylated sugar would be almost 50% which would meet the instant "fucose-free sugar chains is 30% or more or 35% or more".

Therefore, applicant's arguments have not been found persuasive.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Dahle whose telephone number is 571-272-8142. The examiner can normally be reached on 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Ram Shukla can be reached 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Chun Dahle/

Primary Examiner, Art Unit 1644